Effectiveness of Low-Dose Theophylline for the Management of Biomass-Associated COPD

NCT03984188

Document Date: 12/22/2020

INSTRUCTIONS:

Protocol Title
Effectiveness of Low-dose Theophylline for the Management of Biomass-associated COPD

IRB Review History
NA

Objective
Conduct a pilot trial to assess the efficacy of low-dose theophylline intervention among adults with biomass-related COPD. We will conduct a pilot randomized placebo-controlled trial among 100 adults with biomass-related COPD, randomized to either low-dose theophylline or placebo in Nakaseke and Kampala, Uganda. Both arms will have access to salbutamol as needed (standard care). The primary outcome will be one-year change in St. George Respiratory Questionnaire score, an instrument previously validated in this setting. We will collect lung function measurements (forced expiratory volumes) and serum fibrinogen/hs-CRP, as well as 48-hour personal exposure assessments to HAP and demographic questionnaires during one year follow up.

Evaluate incremental cost-effectiveness of theophylline, and explore differences across settings. We will administer the SF-36 quarterly for one year and calculate the incremental cost-effectiveness ratio (ICER) of low-dose theophylline plus salbutamol relative to salbutamol alone, measured as the incremental cost per incremental QALY gained. We will compare the estimated cost-effectiveness of theophylline to traditional benchmarks (e.g. per-capita GDP) as well as revealed willingness-to-pay for other health interventions in Uganda. We will additionally develop a Markov model using lung function decline models to extend cost-effectiveness estimates to other resource-limited settings

Background
Household air pollution (HAP) is the key risk factor for chronic obstructive pulmonary disease (COPD) in LMICs.[1] COPD is a leading cause of morbidity and mortality globally, with over 90% of COPD-related deaths occurring in low- and middle-income countries (LMICs). Household air pollution (HAP) – from burning solid fuels such as wood, dung, agricultural crop waste, and coal for energy – is the primary risk factor for COPD in these settings.[1] Globally, nearly 3 billion people rely on solid fuels (biomass, which includes wood, dung, and agricultural crop waste, or coal) for cooking and heating.[2] Biomass fuel is the main domestic energy source for ~40% of all households and ~90% or rural households in LMICs. Individuals exposed to HAP in LMICs are 41% more likely to have COPD than those without the exposure.[1]

Biomass-related COPD has a distinct histopathology, phenotype and inflammatory profile when compared to tobacco mediated COPD.[3] Individuals with biomass-related COPD demonstrate a different mechanism of injury with increased anthracosis, small airway thickening and peripheral fibrosis on lung biopsy compared to individuals with tobacco smoke mediated COPD.[4, 5] Individuals with biomass-related COPD additionally present with different phenotypes compared to tobacco-related COPD marked by increased cough, phlegm, airway thickening and air trapping, as well as

higher rates of bronchodilator reversibility and hyper responsiveness, signifying an elevated degree of airway inflammation.[1, 5] Biomass-related COPD has a different inflammatory profile with higher circulating levels of CD4 inflammatory mediators (TH2, IL-4 and IL-10) than individuals with tobacco related disease and therefore represent a different endotype.[3] These findings suggest a different response to treatment and disease prognosis compared to tobacco-mediated disease.[3] Despite the high global burden of biomass-associated disease, little is known about the effectiveness of pharmacotherapies for biomass-related COPD; to date, no clinical trials have focused specifically on treatment of biomass-related COPD.[3]

No clinical trials exist related to cost-effectiveness of interventions related to chronic management of COPD in LMICs.[6] Current management guidelines for COPD in LMICs recommend inhaler delivered therapy which is either unavailable or unaffordable in low- and middle-income settings.[6, 7] Effective use of inhaled therapies requires device-specific education, which would not be required with and oral therapy such as theophylline.[8] In one study of eight LMICs, there was no availability of ipratropium inhalers, a key recommended treatment for chronic management of COPD in LMICs.[9] A study among 52 countries found that among 40% of individuals the cost of medication would amount to 1 day of work to purchase a monthly course of salbutamol, above cost-effectiveness benchmarks in LMICs.[10] In several of the countries studied the monthly cost of medications accounted for 4.5 days' wage.[10] A similar study in India found inhaled salbutamol was unaffordable for 80% of the population based on drug pricing and wages.[11] Although no trials have been designed to evaluate the cost-effectiveness of treatment for COPD in LMICs, economic modeling demonstrates that annual per-capita costs for managing COPD with inhaler-based therapy would amount to USD 13,000-14,000 per disability adjusted life year (DALY) averted, well above cost effectiveness benchmarks.[12] An effective, and low cost therapy for the management of COPD is desperately needed to address the growing burden of disease in LMICs.

Inclusion and Exclusion Criteria
Inclusion criteria for the parent study are: 1. Age ≥ 40 years; 2. Full-time resident of Nakaseke or Kampala; 3. Currently using a traditional stove only. Inclusion criteria for this trial include: 1. post-bronchodilator FEV_1/FVC < the lower limit of normal of the Global Lung Initiative Mixed Ethnic reference population [13, 14]; 2. Grade B-D COPD [15] 3. Daily biomass exposure

Exclusion criteria include: 1. Plans to move within one year; 2. Uncontrolled hypertension, 3. Pregnancy (assessed by urine pregnancy test among women of child-bearing age/menstrual history), 4. Current use of chronic respiratory medications (LABA, LAMA, ICS), 5. History of post-treatment pulmonary tuberculosis, 6. ≥10 pack year tobacco smoking history, 7. Known intolerance or contraindication to theophylline.

Number of Subjects
100 Subjects recruited in Uganda

Study-Wide Recruitment Methods
We will enroll participants previously identified with COPD from either the LiNK Cohort Study (Johns Hopkins University IRB00077312) or GeCO Study (Johns Hopkins University IRB00111874). Trained field workers will visit households to contact eligible participants, invite them to the study, and obtain informed consent. Those that agree to

participate will be asked to complete questionnaires and screened for COPD using spirometry for confirmatory testing.

The primary design will be a randomized placebo-controlled trial, for which we will randomize 100 adults into two groups of 50 to receive either daily 200 mg ER low-dose theophylline ("intervention") versus placebo ("control"). Each group will additionally receive standard care per WHO guidelines for management of COPD in LMICs. We will block randomize with a block size of four to each of the two groups using sealed envelopes. We will enroll adults either identified with COPD from the LINK and GeCO study previously conducted in Nakaseke and Kampala, Uganda.

Participants will be enrolled and followed in their homes. Demographic questionnaires will be applied to obtain socioeconomic information, exposure history to cigarettes and household air pollution, occupational exposure, medical history and family history of respiratory illness. Data will be collected by field trained field workers at each site and will be electronically entered into REDCap using tablets computers.[16]

Low-dose theophylline (200 mg ER) will be provided in childproof bottles once a month to participants enrolled in the intervention arm by trained field workers. Medications will be refilled monthly by fieldworkers. Placebo pills will be manufactured in identical packaging and will be provided for individuals with COPD randomized to the control arm. Standard care for COPD per WHO guidelines (salbutamol inhalers as needed) will be provided to both arms prescribed by study clinicians.

Spirometry: Spirometry will be performed on participants at baseline, 6 months, 12 months post-randomization. We have an experienced team of fieldworkers who have conducted previous population-based studies using spirometry.[17] Spirometry will be conducted on all participants before and after bronchodilator therapy (400 mcg of salbutamol using a spacer) following standardized guidelines.[18] We will use the Easy on-PC handheld spirometer (ndd, Zurich, Switzerland), a device that has been validated and used in several large population-based studies.[19, 20] We will record post-bronchodilator PEF, FEV_1, and FVC.

Health-related Quality of Life Measures – The primary outcome of the study will be change in respiratory symptoms (SGRQ) at 12 months. We will additionally measure physical health and mental health domains through the SF-36. We will administer these surveys at baseline, six months and twelve months.

Table 1. Proposed exposure and outcome assessment time table

Study Time Point	(baseline)	3 months	6 months	9 months	12 months
Primary outcomes					
SGRQ	**X**		**X**		**X**
Personal exposure					
48-h $PM_{2.5}$, BC, CO	**X**	**X**	**X**	**X**	**X**
Secondary outcomes					
SF-36	**X**		**X**		**X**
PEF	**X**		**X**		**X**
FEV_1	**X**		**X**		**X**
FVC	**X**		**X**		**X**
Biomarkers	**X**		**X**		**X**
Covariates					

Socio-demographics	**X**				
Clinical history	**X**	**X**	**X**	**X**	**X**
Weight/height/BMI	**X**				
Diet/food security	**X**				

Abbreviations: BC, black carbon; BMI, body mass index CO, carbon monoxide $PM_{2.5}$, fine particulate matter; SF-36, Short Form 36 survey; SGRQ, St. George Respiratory Questionnaire; PEF, peak expiratory flow; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity

Biomarkers: We will validate fibrinogen, an FDA approved biomarker for all-cause mortality and exacerbations among those with COPD, to lung function and COPD exacerbations in our setting.[21-23] We will additionally collect hs-CRP and serum eosinophils. We will conduct blood draws at baseline, six months and twelve months with the aim of assessing response to theophylline as well as identifying sub-groups which may have a differential response to therapy. We will store blood samples in Uganda for future analysis.

HAP Measurements: We will measure personal $PM_{2.5}$ concentrations using the Ultrasonic Personal Air Sampler (UPAS, Access Sensor Technologies, Fort Collins, CO, USA), a gravimetric sampler, and CO using the EL-USB-CO (Lascar Electronics Inc., Eire, PA). $PM_{2.5}$ and CO monitors for personal exposure will be worn near the breathing zones of the index participants. Participants will be encouraged to wear the monitors continuously during the 48-hour period, and to keep close while sleeping. Black carbon content of each personal filter will be determined using a validated optical attenuation measure.[24, 25]

CT Imaging: We will conduct inspiratory and expiratory computerized tomography (CT) scans among study participants at baseline and assess central airway wall thickness (percentage wall area, thickness-to-diameter ratio) if additional funding is obtained. We will aim to assess whether there is a differential response to treatment among those with unique phenotypes of central airway disease. We will only conduct CT scans with amendment to the IRB and informed consent.

Study Timelines
We will follow participants monthly for a one-year period, and enrollment will be staggered over a one-year period.

Study Endpoints
The primary outcomes for this pilot trial at one year include a) difference in SGRQ score between groups;

Secondary outcome variables.
a) difference in lung function decline and airway reversibility; b) differences in health-related quality of life as determined by the SF-36. We will additionally take detailed clinical history to evaluate for frequency and duration of COPD exacerbations, frequency and duration of hospitalization, exacerbation severity and use of additional medications for respiratory illness (i.e. antibiotics or steroids). Patients will keep diary cards to record and symptoms, adverse events, rescue medication, sick days and loss of workdays because of exacerbation.

Procedures Involved
Spirometry
We will use the EasyOne Pro (ndd, Zurich Switzerland)[8,9]. We will follow standard criteria from the ATS for the measurement of DLCO (40), and adjust values of DLCO by altitude and carboxyhemoglobin levels. The device is easy to use and training will be provided for all health workers involved in the study to comply with the 2005 joint European Respiratory Society and American Thoracic Society measurement standards. In addition we will have a centralized quality control system in which we will grade all tests according to published standards.[10] Regular supervision will take place and feedback will be provided to all field workers. We will record forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), as well as store individual flow-volume curves for quality control assessment and further analysis.

We will administer 4 puffs from a salbutamol inhaler (100 mcg / puff) via a spacer and repeat spirometry 10-15 minutes later. We will define reversibility as an improvement of > 12% or > 0.2 L in baseline FEV_1 or FVC. In order to minimize the risks associated with administration of bronchodilator, we will administer only two puffs of salbutamol, rather than the four-puff dose that is more routinely recommended in a clinical setting. In extremely rare cases, a person can have a reaction to salbutamol in the form of a hypersensitivity reaction or cardiac arrhythmia. A trained physician will be available to the research team in the event of an adverse reaction. The study team will monitor heart rate/rhythm, blood pressure and SpO_2. For a cardiac event, patients will be located at the care center. It is important to emphasize that a reaction to salbutamol is extremely rare, and for this reason salbutamol is standard in the treatment and diagnosis of restrictive lung disease. To minimize risks, exclusion criteria for salbutamol use include a pulse greater than 120 beats/minute and BP > 180 (systolic)/100(diastolic).

Low-dose theophylline
Low-dose theophylline has been proposed as a treatment for biomass-related COPD in LMICs.[26] Theophylline has been used in the treatment of chronic obstructive airway diseases, including COPD, for more than 70 years and remains widely prescribed worldwide, largely due to its low expense.[26] In many high-income countries, the frequency of side effects and the drug's narrow therapeutic index has led to reduced usage for management of COPD. However, a number of studies have demonstrated that theophylline at lower doses (1-5mg/L) results in improved respiratory symptoms via transcriptional downregulation of inflammatory genes.[27-29] Therapeutic monitoring is not necessary at such doses. Previous studies among individuals with tobacco-related COPD have demonstrated low-dose theophylline monotherapy results in improved lung function (FEV_1), respiratory symptoms and decreased the frequency and duration of exacerbations.[30] Theophylline may prove to be an effective therapy for biomass-related COPD given availability, low cost, and anti-inflammatory mechanism of action.[26, 31]

Computerized tomography Scans (CT)
Participants will undergo CT scans of the chest as follows. Inspiratory Views: 1–1.5 mm collimation at 2 cm intervals in full inspiration. High spatial frequency reconstruction

algorithm (can use bone algorithm on GE machine) with window levels at mediastinum 440 width, level 40 and lung 1000 width, level –700.
Prone Images: Performed with 1–1.5 mm collimation at 2 cm intervals in full inspiration as noted above
Expiratory Views: 3 post expiratory views with 1–1.5 mm collimation at end expiration following a forced vital capacity maneuver. Expiratory views are performed at the level of the aortic arch, the tracheal carina, and above the diaphragm. The scanner will be subjected to a monthly quality assessment with a phantom check including uniformity, linearity, and noise. In addition, we will ensure engineering check of spatial and contrast resolution and an annual medical physics check every 6 months.

Data and Specimen Banking
Serum samples will be stored in Uganda for future analysis and will be accessible by members of the study staff.

Data Management
We will determine whether low-dose theophylline intervention results in improved self-reported respiratory symptoms (SGRQ) compared to standard care. For repeated outcome measurements (e.g., SGRQ, PEF, FEV_1, FVC), linear mixed effects models will be used to account for within-subject correlation. The main analysis will be by intention to treat (ITT), based on cases where the primary outcome is available and will therefore rely on an assumption that data is missing at random. We will describe the number (%) with missing primary outcome, look at reasons for missingness and consider characteristics of the patients excluded from the ITT analysis at 12 months. Multiple imputation for the primary analysis will be used if the missing data exceeds 10% of randomized patients. Exposures will be aggregated to represent chronic exposure as determined by the health outcomes. We will utilize regression analysis for longitudinal outcomes. We will use generalized estimated equations for repeated measurements.

We will examine repeated measurements of SGRQ by treatment group and carry out exploratory analyses to consider effects of the intervention over time. The SGRQ has previously been shown to have a standard deviation of 20 points in a similar population and a minimal clinical important difference of 4 points (a previous study involving low-dose theophylline resulted in a 7.8 point difference between intervention and control).[30] A sample of 80 participants with COPD total will be needed to produce an 80% one-sided confidence interval that excludes a 4-point difference in SGRQ under the scenario of a 7.8 point difference in means.[32] Of the 150 individuals we will contact with COPD from our existing cohort and trial, I expect 75% to have Grade B-D COPD based on our previous studies. Of those we can expect 10% to decline to participate and an additional 10% who will drop out of the trial over a year based on our previous experience. With conservative estimates I expect to have 90 participants (45 per arm) who will complete the pilot trial.

We will additionally compare exposure-response relationship between HAP and FEV_1 between groups to assess whether theophylline attenuates exposure-response associations. For the exposure-response associations, analyses will be conducted within the intervention and the control groups separately, as well as in a combined analysis. Non-linear associations between exposure and health outcomes will be examined using generalized additive models and other spline-based approaches.[33]

.

Provisions to Monitor the Data to Ensure the Safety of Subjects
We will collect data on safety and tolerability of theophylline and placebo. We will utilize study clinicians for reporting and evaluation. Study participants will be educated on detecting arrhythmias (i.e. persistent supraventricular tachycardia) and will be instructed to call the on-call study clinician with any event. We will maintain a data safety and monitoring board with reporting of all serious adverse events (including seizure) within 24 hours by a study clinician. We will utilize health monitoring infrastructure of ongoing studies (GeCO) to adjudicate adverse events. Health centers will be identified based on participants' residence and patients will be referred and transported for health-related events.

Plan for reporting unanticipated problems or study deviations.
In addition to the protection of human subjects and minimization of risks detailed above, we will convene a Data Safety Monitoring Board (DSMB) for this study. Investigators will record pertinent data on all reportable adverse events using an adverse event report form. These forms will include the following information: 1) an estimation of event severity (mild, moderate, serious), 2) if a therapeutic intervention was necessary to prevent permanent impairment or damage, 3) if there was an immediate threat of death due to the event, 4) if the event was unexpected or more severe than expected, 5) if there was a causal relationship to study procedures, 6) if the patient was withdrawn from study procedures because of the event, 7) status of the adverse event at the time of initial adverse event report, and 8) final outcome of the adverse event. Reportable adverse event forms will be submitted to the Johns Hopkins Institutional Review Board and to the DSMB. Serious adverse events will be reported to the IRB and DSMB by telephone or e-mail within 7 days of discovery of the event.

There will be no interim analysis conducted and no early stopping rules for the trial

Withdrawal of Subjects
There is no definition for treatment failure. Participants will be removed from the study if they chose to no longer participate or there is loss to follow up on two subsequent visits.

Risks to Subjects
Medical risks, listing all procedures, their major and minor risks and expected frequency.
Low-dose theophylline at therapeutic levels of <10 mg/L is well tolerated with minimal adverse side effects compared to standard therapeutic levels (10-20 mg/L).[34] In previous trials there were no significant differences between low-dose theophylline and placebo group. The most frequent drug-related adverse effects were stomach discomfort, headache, insomnia and palpitations. Other serious side effects include potential seizure. Blood draws are generally safe and well tolerated; the risk include bruising, infection at puncture site and pain or discomfort.

Steps taken to minimize the risks.
For spirometry to minimize the risk of injury associated with fainting, the maneuver is performed with participants seated in a stationary chair. Technicians administering the test will be trained to watch for signs of faintness and to stop the test if the participant appears unusually breathless or uncomfortable. There is no risk of cross-contamination or infection as disposable mouthpieces will be used. Questions are also asked to screen out those people who have or recently had conditions that place them at risk when doing

spirometry (including recent myocardial infarction; eye, chest, or abdominal surgery; and tachycardia). Participants with current respiratory symptoms will be asked to re-schedule their appointment.

To minimize the risks associated with administration of bronchodilator, we will administer only two puffs of salbutamol, rather than the four-puff dose that is more routinely recommended in a clinical setting. In extremely rare cases, a person can have a reaction to salbutamol in the form of a hypersensitivity reaction or cardiac arrhythmia. The study team will monitor heart rate/rhythm, blood pressure and SpO_2. For a cardiac event, we will transport any patient to the nearest capable care center. It is important to emphasize that a reaction to salbutamol is extremely rare, and for this reason salbutamol is standard in the treatment and diagnosis of restrictive lung disease. To minimize risks, exclusion criteria for salbutamol use include a pulse greater than 120 beats/minute and BP > 180 mmHg (systolic)/100 mmHg (diastolic). To minimize the risk associated with blood draw, we will use disposable materials for each procedure, which significantly reduces the risk of disease transmission. In addition, the study staff is trained in sampling, reducing the risks and complications. Also, established standard procedures in the art of venipuncture and antisepsis and biosecurity measures will be followed.

Financial risks to the participants.
There are no anticipated financial risks to participants. LD-theophylline has been well studied in both high- and low-income settings with minimal side effects.[30, 35] Among these previous studies there have been no reported serious adverse events related to the medication.

Potential Benefits to Subjects
This will be one of the first studies to evaluate the effectiveness and cost-effectiveness of chronic pharmacotherapy for biomass-related COPD. The high prevalence (~40%) of biomass fuel use globally and association between HAP and COPD make the potential impact of this intervention of high importance. Additionally, this study will provide a framework and tools for designing and adapting RCTs to evaluate the effectiveness of chronic medical therapy for other respiratory diseases. Our relationships with Ugandan government stakeholders and international organizations increase the potential impact and reach of our research.

Vulnerable Populations

Vulnerable populations will not be included in this study

Multi-Site Research
Study activities will occur in Nakaseke and Kampala, Uganda. All study activities have been approved by the Makerere College of Health Sciences School of Medicine IRB and the Uganda Council of Science and Technology. Data analysis will occur in Uganda and at the University of Miami. All IRBs will be updated with changes in the protocol. All sites will safeguard data using encrypted cloud software. All data will remain deidentified

unless required by the DSMB. There will be no interim analysis unless specified by the DSMB.

Community-Based Participatory Research
Study design and approach was conducted in collaboration with the African Center for Social Sustainability (https://accessuganda.org), a community-based health organization which aims to empower the local rural community through education, healthcare and economic programs. Results will be disseminated in coordination with ACCESS Uganda to the community and Ugandan Ministry of Health.

Sharing of Results with Subjects
Study participants will have results shared at the conclusion of the trial. Study staff will be available to answer any questions.

Setting
The study will take place in Nakaseke and Kampala, Uganda. Recruitment and follow up will occur at Nakaseke General Hospital and Makerere Lung Institute for all medical testing and follow up. Air pollution measurements will be taken at prespecified time points in participant's houses.

Resources Available
Recruitment will be undertaken by two Ugandan physicians (Drs. Patricia Alupo and Esther Namazzi). Additionally, and independent study clinician (Dr. Richard Munana) will oversee theophylline levels and independently report adverse events. Theophylline and salbutamol will be dispensed by the Makerere Lung Institute with a trained pharmacist. Phlebotomy will be conducted by qualified nurses and spirometry and air pollution monitoring will be conducted by qualified research personnel. All staff will be hired through the Makerere Lung Institute that will oversee recruitment, good clinical practices, and data quality and control.

Prior Approvals
Approval for the following protocol has been obtained by the Makerere College of Health Sciences School of Medicine IRB (REF 2020-093) as well as the Johns Hopkins School of Medicine IRB (IRB 00209008).

Recruitment Methods
We will enroll participants previously identified with COPD from either the LiNK Cohort Study (Johns Hopkins University IRB00077312) or GeCO Study (Johns Hopkins University IRB00111874). Trained field workers will visit households to contact eligible participants, invite them to the study, and obtain informed consent. Those that agree to participate will be asked to complete questionnaires and screened for COPD using spirometry for confirmatory testing. Participants will be paid $5 at baseline, 6 months and 12 months visit to compensate for time required to complete questionnaires and obtain

additional studies ($15 total per participant). There will be no reduction or penalties for not completing the study

Local Number of Subjects
No subjects will be recruited at the University of Miami

Confidentiality
We do not anticipate legal risks related to breach of confidentiality for participants in Uganda. We will set up several mechanisms to ensure the confidentiality of data collected from the participants. Confidentiality of all responses will be the highest priority for the research team. The site coordinator will assign a unique identification code to the participant once enrolled in the study. This number will be used to identify the case on all hard and electronic copy documents and will be part of the survey data that is entered. Name of and telephone numbers to contact participants and caregivers will not appear on the questionnaires or questionnaire data files.
Choose the statements below that are applicable to this research:

26(a). Will the research collect protected health information or personally identifiable information from the EMR or from subjects at UHealth and/or JHS?

☐ Yes (If checked go to 26(b))

☒ No (If checked, go to Section 27)

26(b). Check the box next to the correct statement below

☐ Research Subjects will sign a HIPAA Authorization before the research will collect this data.

☒ Research Subjects will not sign a HIPAA Authorization for this data collection and the research is requesting a waiver of HIPAA authorization from the IRB.

26(c). How will the research store the data?

☐ On a University of Miami electronic device (e.g. encrypted, password-protected computer)

☒ On a cloud-based storage system that is approved by the University of Miami

☐ On the secured JHS SharePoint environment

☐ Other, specify: Click here to enter text.

26(d) Select one of the following:

☐ The Principal Investigator (and/or Study Team members) will record (e.g. write down, abstract) data acquired in a manner that does not include any indirect or direct identifiers (listed in the instructions for Section 26 of this protocol), and the recorded data will not be linked to the individual's' identity.

OR

☒ The Principal investigator (and/or Study Team members) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers (see list in the instructions for Section 26 of this protocol) of any subject. Instead, the

Principal Investigator and/or Study Team members shall will assign a code (that is not derived in whole or in part from any direct or indirect identifiers of the individual) to each study subject and link the code to the study subject's identity. The link to each subject's identity and/ or other identifiable information will be maintained on a document separate from the research data.

26(e) Additional requirement for Jackson Health System Data:

☒ Not-applicable, no data will be acquired from JHS under a waiver of authorization.

☐ JHS data, including Protected Health Information (PHI) and/or Personally Identifiable Information (PII), acquired from JHS for this research under a waiver of authorization shall only be stored on the secured JHS SharePoint environment made available by JHS. I and the Study Team members shall not copy or store the JHS sourced personally identifiable information (PII), including protected health information (PHI) data to any other system, including any systems maintained or provided by the University of Miami. I and the Study Team shall only copy or transfer JHS-sourced data that has been properly de-identified in accordance with all requirements contained in the HIPAA Rules by removing all of the identifiers listed in the instructions for Section 26 of this protocol.

27. Biospecimens

☐ Not applicable. No biospecimens will be collected

☐ *Bio*-Specimens obtained for this research will be stored without any direct or indirect identifiers.

☒ *Bio*-Specimens obtained for this research will be stored in a de-identified coded manner.

☐ When required to transport data or bio-specimens for this research, the research team will transport the data and bio-specimens in a de-identified (or anonymous) manner with a link to the individual subject's identity maintain separately from the data and/or bio-specimen.

Provisions to Protect the Privacy Interests of Subjects

All data will be deidentified and blinded to study investigators other than independent study clinician and study pharmacist for the purposes of adverse event reporting. We will set up several mechanisms to ensure the confidentiality of data collected from the participants. Confidentiality of all responses will be the highest priority for the research team. The site coordinator will assign a unique identification code to the participant once enrolled in the study. This number will be used to identify the case on all hard and electronic copy documents and will be part of the survey data that is entered. Name of and telephone numbers to contact participants and caregivers will not appear on the questionnaires or questionnaire data files.

Compensation for Research-Related Injury

Trial insurance will be provided by Goldstar Insurance Co Ltd. (CTI/GSI/KA/100002/2020) for 36 months with a 12 mo extended reporting period. The liability of the underwriters shall not exceed USD 100,000 per loss and in the aggregate for any one period of insurance.

Economic Burden to Subjects

Participants will not incur costs related to study drugs or procedures. All costs will be accounted for through the parent grant mechanism (1K23HL146946; PI: Siddharthan).

Consent Process

We will enroll participants previously identified with COPD from either the LiNK Cohort Study (JHU IRB00077312) or GeCO Study (JHU IRB00111874). Trained field workers will visit households to contact eligible participants, invite them to the study, and obtain informed consent in either English or Luganda. Those that agree to participate will be asked to complete questionnaires and screened for COPD using spirometry for confirmatory testing.

☒Not applicable. This research will not collect data from JHS record under a waiver of authorization

Notwithstanding the preceding "I confirm" statements above, I agree that neither I nor any member of the study team listed on the IRB submission for this Protocol shall ever re-use or re-disclose any of the information acquired from Jackson Health System in any format, whether **identifiable or de-identified,** to any individual or entity without first obtaining written permission from Jackson Health System, even if such re-use or re-disclosure is permissible by law (e.g., HIPAA).

12/18/2020

PI Signature Date

Drugs or Devices

Study drugs will be delivered to Makerere Lung Institute. Low-dose theophylline (Unicontin 400mg) and salbutamol inhalers will be provided by SurgiPharm in Kampala. Identical placebo tablets will be manufactured and delivered by Kampala Pharmaceutical Industries. Study drugs will be stored in locked cabinets. Medications will be allocated to pill containers monthly, labeled with participant names and date. Allocation will be based on a master list of participants and allocation group that will be only accessible to trial pharmacist (Ivan Segawa) and local safety clinician (Richard Munana).

1. Siddharthan, T., et al., *Association Between Household Air Pollution Exposure and Chronic Obstructive Pulmonary Disease Outcomes in 13 Low-and Middle-income Country Settings.* American journal of respiratory and critical care medicine, 2018(ja).
2. Bonjour, S., et al., *Solid fuel use for household cooking: country and regional estimates for 1980-2010.* Environmental Health Perspectives, 2013. **121**(7): p. 784-90.
3. Pérez-Padilla, R., A. Ramirez-Venegas, and R. Sansores-Martinez, *Clinical characteristics of patients with biomass smoke-associated COPD and chronic bronchitis, 2004-2014.* Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation, 2014. **1**(1): p. 23.
4. Rivera, R., et al., *Comparison of lung morphology in COPD secondary to cigarette and biomass smoke.* The International Journal of Tuberculosis and Lung Disease, 2008. **12**(8): p. 972-977.
5. Moran-Mendoza, O., et al., *Wood smoke-associated lung disease: a clinical, functional, radiological and pathological description.* The International Journal of Tuberculosis and Lung Disease, 2008. **12**(9): p. 1092-1098.
6. Beran, D., et al., *Burden of asthma and chronic obstructive pulmonary disease and access to essential medicines in low-income and middle-income countries.* The Lancet Respiratory Medicine, 2015. **3**(2): p. 159-170.
7. Mendis, S., et al., *The availability and affordability of selected essential medicines for chronic diseases in six low-and middle-income countries.* Bulletin of the world health organization, 2007. **85**(4): p. 279-288.
8. Fink, J.B. and B.K. Rubin, *Problems with inhaler use: a call for improved clinician and patient education.* Respiratory care, 2005. **50**(10): p. 1360-1375.
9. Mendis, S., et al., *Gaps in capacity in primary care in low-resource settings for implementation of essential noncommunicable disease interventions.* International journal of hypertension, 2012. **2012**.
10. Lessing, C., C. Mace, and K. Bissell, *The availability, pricing and affordability of three essential asthma medicines in 52 low-and middle-income countries.* Pharmacoeconomics, 2013. **31**(11): p. 1063-1082.
11. Kotwani, A., *Availability, price and affordability of asthma medicines in five Indian states.* The International Journal of Tuberculosis and Lung Disease, 2009. **13**(5): p. 574-579.
12. Stanciole, A.E., et al., *Cost effectiveness of strategies to combat chronic obstructive pulmonary disease and asthma in sub-Saharan Africa and South East Asia: mathematical modelling study.* Bmj, 2012. **344**: p. e608.
13. Miller, M.R., et al., *Standardisation of spirometry.* Eur respir J, 2005. **26**(2): p. 319-38.
14. Quanjer, P.H., et al., *Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations.* European Respiratory Journal, 2012. **40**(6): p. 1324-1343.
15. Vogelmeier, C.F., et al., *Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease 2017 report.* Respirology, 2017. **22**(3): p. 575-601.

16. Harris, P.A., et al., *Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support.* Journal of biomedical informatics, 2009. **42**(2): p. 377-381.
17. Jaganath, D., et al., *Prevalence of chronic obstructive pulmonary disease and variation in risk factors across four geographically diverse resource-limited settings in Peru.* Respiratory research, 2015. **16**(1): p. 40.
18. Miller, M.R., et al., *Standardisation of spirometry.* European respiratory journal, 2005. **26**(2): p. 319-338.
19. Jaganath, D., et al., *Prevalence of chronic obstructive pulmonary disease and variation in risk factors across four geographically diverse resource-limited settings in Peru.* Respiratory research, 2015. **16**(1): p. 40.
20. Buist, A.S., et al., *International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study.* The Lancet, 2007. **370**(9589): p. 741-750.
21. Duvoix, A., et al., *Blood fibrinogen as a biomarker of chronic obstructive pulmonary disease.* Thorax, 2013. **68**(7): p. 670-676.
22. Mannino, D.M., et al., *Plasma fibrinogen as a biomarker for mortality and hospitalized exacerbations in people with COPD.* Chronic obstructive pulmonary diseases (Miami, Fla.), 2015. **2**(1): p. 23.
23. Mannino, D.M., et al., *Fibrinogen, COPD and mortality in a nationally representative US cohort.* COPD: Journal of Chronic Obstructive Pulmonary Disease, 2012. **9**(4): p. 359-366.
24. Ahmed, T., et al., *Measurement of black carbon (BC) by an optical method and a thermal-optical method: Intercomparison for four sites.* Atmospheric Environment, 2009. **43**(40): p. 6305-6311.
25. Baumgartner, J., et al., *Highway proximity and black carbon from cookstoves as a risk factor for higher blood pressure in rural China.* Proc Natl Acad Sci U S A, 2014. **111**(36): p. 13229-34.
26. Barnes, P.J., *Theophylline in chronic obstructive pulmonary disease: new horizons.* Proceedings of the American Thoracic Society, 2005. **2**(4): p. 334-339.
27. Cosio, B.G., et al., *Low-dose theophylline enhances the anti-inflammatory effects of steroids during exacerbations of COPD.* Thorax, 2009. **64**(5): p. 424-429.
28. Ford, P.A., et al., *Treatment effects of low-dose theophylline combined with an inhaled corticosteroid in COPD.* Chest, 2010. **137**(6): p. 1338-1344.
29. Barnes, P.J., *Theophylline.* American journal of respiratory and critical care medicine, 2013. **188**(8): p. 901-906.
30. Zhou, Y., et al., *Positive benefits of theophylline in a randomized, double-blind, parallel-group, placebo-controlled study of low-dose, slow-release theophylline in the treatment of COPD for 1 year.* Respirology, 2006. **11**(5): p. 603-610.
31. Checkley, W., et al., *Management of NCD in low-and middle-income countries.* Global heart, 2014. **9**(4): p. 431-443.
32. Cocks, K. and D.J. Torgerson, *Sample size calculations for pilot randomized trials: a confidence interval approach.* Journal of clinical epidemiology, 2013. **66**(2): p. 197-201.
33. Hastie, T. and R. Tibshirani, *Generalized additive models for medical research.* Stat Methods Med Res, 1995. **4**(3): p. 187-96.

34. Devereux, G., et al., *Use of low-dose oral theophylline as an adjunct to inhaled corticosteroids in preventing exacerbations of chronic obstructive pulmonary disease: study protocol for a randomised controlled trial.* Trials, 2015. **16**(1): p. 267.
35. Singh, M., et al., *Effect of low dose theophylline as adjunct in treatment of COPD*. 2016, Eur Respiratory Soc.